PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 05 July 2001 (05.07.01)	
International application No. PCT/JP00/06874	**Applicant's or agent's file reference** PWO-20338
International filing date (day/month/year) 02 October 2000 (02.10.00)	**Priority date** (day/month/year) 04 October 1999 (04.10.99)
Applicant MORIGUCHI, Akira et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

07 April 2001 (07.04.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer H. Zhou
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
PWO-20338		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/JP 00/06874	02/10/2000	04/10/1999
Applicant		
FUJISAWA PHARMACEUTICAL CO., LTD.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 00/06874

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/39 //(A61K38/39,31:445)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	MAEDA MASASHI ET AL: "FK506 (tacrolimus) as a potential anti-stroke agent (3): Increased therapeutic efficacy with combined treatment of FK506 and recombinant tissue plasminogen activator (rt-PA) in a rat stroke model." JAPANESE JOURNAL OF PHARMACOLOGY, vol. 82, no. Suppl. 1, 2000, page 174P XP000990982 73rd Annual Meeting of the Japanese Pharmacological Society.;Yokohama, Japan; March 23-25, 2000 ISSN: 0021-5198 * See Abstracts P217-P219, and in particular P218 * --- -/--	1-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 May 2001	21/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Veronese, A

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	YAGITA Y ET AL: "EFFECT OF IMMUNOSUPRESSANT FK506 ON ISCHEMIA-INDUCED DEGENERATION OF HIPPOCAMPAL NEURONS IN GERBILS" LIFE SCIENCES,PERGAMON PRESS, OXFORD,GB, vol. 59, no. 19, 1996, pages 1643-1650, XP000980211 ISSN: 0024-3205 the whole document	1-15
Y	TOUNG THOMAS J ET AL: "Neuroprotective FK506 does not alter in vivo nitric oxide production during ischemia and early reperfusion in rats." STROKE, vol. 30, no. 6, June 1999 (1999-06), pages 1279-1285, XP000980399 ISSN: 0039-2499 the whole document	1-15
Y	BOCHELEN D ET AL: "CALCINEURIN INHIBITORS FK506 AND SDZ ASM 981 ALLEVIATE THE OUTCOME OF FOCAL CEREBRAL ISCHEMIC/REPERFUSION INJURY" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS,AMERICAN SOCIETY FOR PHARMACOLOGY AND,US, vol. 288, no. 2, February 1999 (1999-02), pages 653-659, XP000980203 ISSN: 0022-3565 the whole document	1-15
Y	KIM YANG-HEE ET AL: "Nonproteolytic neuroprotection by human recombinant tissue plasminogen activator." SCIENCE (WASHINGTON D C), vol. 284, no. 5414, 23 April 1999 (1999-04-23), pages 647-650, XP002164663 ISSN: 0036-8075 the whole document	1-15
Y	BEDNAR M M ET AL: "COMBINATION TISSUE PLASMINOGEN ACTIVATOR AND TICLOPIDINE THERAPY INA RABBIT MODEL OF ACUTE THROMBOEMBOLIC STROKE" NEUROLOGICAL RESEARCH,XX,XX, vol. 18, no. 1, 1 February 1996 (1996-02-01), pages 45-48, XP000646532 the whole document	1-15
Y	US 5 945 432 A (BEDNAR MARTIN M ET AL) 31 August 1999 (1999-08-31) the whole document	1-15

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 00/06874

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 648 351 A (KELLY JOHN S ET AL) 15 July 1997 (1997-07-15) the whole document ---	1-15
A	BUNDICK ET AL: "FK506 AS AN AGONIST TO INDUCE INHIBITION OF INTERLEUKIN 2 PRODUCTION" TRANSPLANTATION,US,WILLIAMS AND WILKINS, BALTIMORE, MD, vol. 53, no. 5, 1992, pages 1150-1153, XP000913592 ISSN: 0041-1337 the whole document -----	1-15

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-15 relate to a rather large number of possible compounds, which are defined by reference to pharmacological mechanisms of action: The expression: "use of a plasminogen activator for manufacturing a medicament for increasing an effect caused by IL-2 inhibitor" in claim 1 and "use of IL-2 inhibitor for manufacturing a medicament for increasing or decreasing the effect caused by plasminogen activator" in claim 12 defines compounds by reference to pharmacological mechanisms of action; in the present context this wording is considered to lead to a lack of clarity within the meaning of Art. 6 PCT. It is impossible to fully compare the parameters the applicant has chosen to employ with what is set out in the prior art.
Support and/or disclosure within the meaning of Articles 5,6 PCT is to be found however for only a very small proportion of the compounds claimed. Consequently, the search has been carried out for those parts of the claims which appear to be clear, concise, supported and disclosed, namely for the combined, simultaneous, separate or sequential use of FK506 or cyclosporine, and tissue-type plasminogen activator (t-PA,) in relation to a neuroprotective therapy, for the treatment and the prevention of neurodegenerative diseases, and cerebral ischemic diseases, with due regard to the general idea underlying the application.

All claims 1 to 15 have been searched incompletely.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 00/06874

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5945432 A	31-08-1999	NONE	
US 5648351 A	15-07-1997	AU 687025 B	19-02-1998
		AU 5716094 A	19-07-1994
		CA 2152803 A	07-07-1994
		CN 1103580 A,B	14-06-1995
		EP 0676961 A	18-10-1995
		WO 9414443 A	07-07-1994
		JP 8505136 T	04-06-1996
		JP 3038920 B	08-05-2000

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

To:

TABUSHI, Eiji
Fujisawa Pharmaceutical Co., Ltd.
Osaka Factory
1-6, Kashima 2-chome
Yodogawa-ku, Osaki-shi
Osaka 532-8514
JAPON

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year) 17 November 2000 (17.11.00)	
Applicant's or agent's file reference PWO-20338	**IMPORTANT NOTIFICATION**
International application No. PCT/JP00/06874	International filing date (day/month/year) 02 October 2000 (02.10.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 04 October 1999 (04.10.99)
Applicant FUJISAWA PHARMACEUTICAL CO., LTD. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
04 Octo 1999 (04.10.99)	PQ3249	AU	06 Nove 2000 (06.11.00)
15 Febr 2000 (15.02.00)	PQ5643	AU	06 Nove 2000 (06.11.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

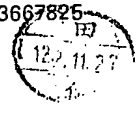
Authorized officer

Magda BOUACHA

Telephone No. (41-22) 338.83.38

Form PCT/IB/304 (July 1998)

003667825



PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
TABUSHI, Eiji
Fujisawa Pharmaceutical Co., Ltd.
Osaka Factory
1-6, Kashima 2-chome
Yodogawa-ku, Osaka-shi
Osaka 532-8514
JAPON

Date of mailing (day/month/year) 12 April 2001 (12.04.01)		
Applicant's or agent's file reference PWO-20338		**IMPORTANT NOTICE**
International application No. PCT/JP00/06874	**International filing date** (day/month/year) 02 October 2000 (02.10.00)	**Priority date** (day/month/year) 04 October 1999 (04.10.99)
Applicant FUJISAWA PHARMACEUTICAL CO., LTD. et al		

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   EP,JP

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   12 April 2001 (12.04.01) under No. WO 01/24784

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PWO-20338		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP00/06874	02/10/2000	04/10/1999
International Patent Classification (IPC) or national classification and IPC A61K31/00		
Applicant FUJISAWA PHARMACEUTICAL CO., LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07/04/2001	23.01.2002
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Bochelen, D Telephone No. +49 89 2399 8150

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/JP00/06874

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-18 as originally filed

Claims, No.:

1-15 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 7-8, 13 with regard to industrial applicabity; 1-15 (partly).

because:

☒ the said international application, or the said claims Nos. 7-8, 13 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-15 (partly).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8, 10, 12-13
	No:	Claims	9, 11, 14-15
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-6, 9-12, 14-15

No: Claims

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. A partial search report was established for the subject-matter of **claims 1-15**. The applicant is informed that no International Preliminary Report will be established in respect of subject-matter which is not covered by the search report (Rule 66(1)(e) PCT).

2. **Claims 7, 8 and 13** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D2: YAGITA Y ET AL: 'EFFECT OF IMMUNOSUPRESSANT FK506 ON ISCHEMIA-INDUCED DEGENERATION OF HIPPOCAMPAL NEURONS IN GERBILS' LIFE SCIENCES,PERGAMON PRESS, OXFORD,GB, vol. 59, no. 19, 1996, pages 1643-1650, XP000980211 ISSN: 0024-3205

D3: TOUNG THOMAS J ET AL: 'Neuroprotective FK506 does not alter in vivo nitric oxide production during ischemia and early reperfusion in rats.' STROKE, vol. 30, no. 6, June 1999 (1999-06), pages 1279-1285, XP000980399 ISSN: 0039-2499

D4: BOCHELEN D ET AL: 'CALCINEURIN INHIBITORS FK506 AND SDZ ASM 981 ALLEVIATE THE OUTCOME OF FOCAL CEREBRAL ISCHEMIC/REPERFUSION INJURY' JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS,AMERICAN SOCIETY FOR PHARMACOLOGY AND,US, vol. 288, no. 2, February 1999 (1999-02), pages 653-659, XP000980203 ISSN: 0022-3565

D5: KIM YANG-HEE ET AL: 'Nonproteolytic neuroprotection by human

recombinant tissue plasminogen activator.' SCIENCE (WASHINGTON D C), vol. 284, no. 5414, 23 April 1999 (1999-04-23), pages 647-650, XP002164663 ISSN: 0036-8075

D6: BEDNAR M M ET AL: 'COMBINATION TISSUE PLASMINOGEN ACTIVATOR AND TICLOPIDINE THERAPY INA RABBIT MODEL OF ACUTE THROMBOEMBOLIC STROKE' NEUROLOGICAL RESEARCH,XX,XX, vol. 18, no. 1, 1 February 1996 (1996-02-01), pages 45-48, XP000646532

D9: US-A-5 648 351 (KELLY JOHN S ET AL) 15 July 1997 (1997-07-15)

3. **Novelty (Art. 33 (1) and (2) PCT)**:

3.1 Document D9 discloses compositions comprising IL-2 inhibitors, i.e macrolides like FK506, and the use thereof for the treatment of cerebral ischemia (D9: col1 l38-42, col 7 example 1 claims 1-4). Documents D5 and D6 disclose compositions comprising tPA and the use thereof for neuroprotection (D5: p649 fig4, p650 col1 §2; D6: p46 col1 §4).
It is stressed that an intended use in a claim directed to a product (**claims 9 and 14**) does not delimit the subject-matter of the claim from the prior art. The label or written material in the package that is subject-matter of **claims 11 and 15** is not a technical feature that would delimit the subject-matter of said claim from the prior art. Consequently it appears that the subject-matter of **claims 9, 11 and 14-15** is anticipated by the prior art.

3.2 The prior art does not disclose compositions comprising a combination of a plasminogen activator and an IL-2 inhibitor nor the use thereof for achieving neuroprotection. Hence, the subject-matter of **claims 1-8, 10 and 12-13** are considered to be new.

4. **Inventive step (Art. 33 (1) and (3) PCT)**:

4.1 The present application relates to the combination of plasminogen activator and IL-2 inhibitors to achieve neuroprotection. The prior art discloses the neuroprotective effect of IL-2 inhibitors, e.g. tacrolimus, cyclosporin A, in various animal models of neurodegeneration (see D2: p1646 fig.1; D3: p1282; D4: p1999

col1 1 §2; D9: col1 l38-42). The neuroprotective effect of tissue plasminogen activator is disclosed in document D5 (D5 p649 fig4, p650 col1 §2). It would be obvious for a skilled man to combine an IL-2 inhibitor with a plasminogen activator to achieve neuroprotection.
It is stressed that the combination of known pharmaceutical compounds in order to obtain the same therapeutical effect as the compounds per se, involves an inventive step only if there is an unexpected advantage over the prior art. This seems not to be the case since the results provided in the application show merely an additive effect of the compounds used.
Consequently, it is considered that the subject-matter of **claims 1-8, 10, 12-13** does not involve an inventive step.

5. **Industrial applicability (Art. 33 (1) and (4) PCT):**

For the assessment of the present **claims 7-8 and 13** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII
Certain observations on the international application

6. **Claims 1-15** do not meet the requirement of Article 6 PCT in that the scope of said claims is not clear. The substances that fall within the scope of said claims are not clearly defined since no pharmacological criteria, e.g. IC_{50}, is indicated for the selection of potential active compounds, thus rendering the scope of **claims 1-15** obscure. Moreover, the definition encompasses a large number of compounds and the disclosure is not sufficiently precise for the person skilled in the art to reduce the technical features to practice without undue burden.

7. It is not clear which therapeutic applications are meant by increasing an effect

caused by IL-2 inhibitor (**claims 1, 7 and 11**) or increasing or decreasing an effect caused by plasminogen activator (**claims 14-15**). Therefore, the subject-matter of **claims 1, 7, 11 and 14-15** is not clearly defined (Art. 6 PCT).